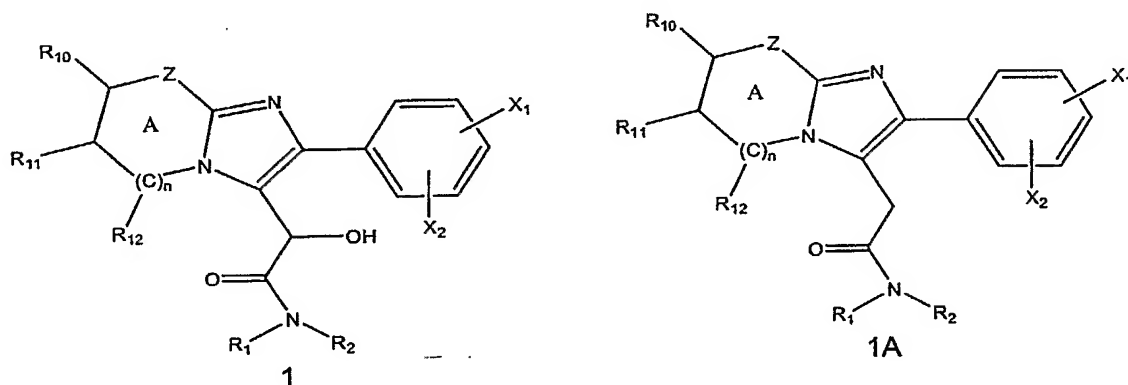


CLAIMS

What is claimed is:

1. A process for the preparation of a heteroaryl acetamide from a heteroaryl α -hydroxyacetamide, the process comprising directly hydrogenating a heteroaryl α -hydroxyacetamide in the presence of hydrogen gas in a reaction mixture comprising a solvent system, the heteroaryl α -hydroxyacetamide, at least one strong acid, a halide and a catalyst, wherein the reaction mixture has a molar ratio of the starting heteroaryl α -hydroxyacetamide to water at the initiation of hydrogenolysis of at least about 2:1, the heteroaryl α -hydroxyacetamide corresponding to Formula 1 and the heteroaryl acetamide product corresponding to Formula 1A:



wherein

Z is O, NR₂₀ or CR₂₁;

X₁ and X₂ are independently selected from the group consisting of hydrogen, halogen, C₁₋₄ alkoxy, C₁₋₆ alkyl, -CF₃ and CH₃SO₂-;

R₁ and R₂ are independently hydrogen or hydrocarbonyl;

R₁₀ is hydrogen, halogen, C₁₋₄ alkyl, or a member of a fused ring wherein the fused ring is (i) a substituted or unsubstituted, saturated or unsaturated, five or six-membered, heterocyclic or carbocyclic ring fused to the A ring comprising R₁₀, the carbon atom to which R₁₀ is attached, R₂₀, and the nitrogen atom to which R₂₀ is attached, or (ii) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R₁₀, R₁₁, and the carbon atoms to which R₁₀ and R₁₁ are attached, optionally substituted with Y at a substitutable position thereof;

R₁₁ is hydrogen, halogen, C₁₋₄ alkyl, or a member of a fused ring wherein the fused ring is (i) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R₁₀, R₁₁, and the carbon atoms to which R₁₀ and R₁₁ are attached, optionally substituted with Y at a substitutable position thereof, or (ii) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R₁₁, R₁₂, and the carbon atoms to which R₁₁ and R₁₂ are attached, optionally substituted with Y at a substitutable position thereof;

R₁₂, if present, is hydrogen, halogen, C₁₋₄ alkyl, or a member of a fused ring wherein the fused ring is (i) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R₁₁, R₁₂, and the carbon atoms to which R₁₁ and R₁₂ are attached, optionally substituted with Y at a substitutable position thereof;

R₂₀ is C₁₋₅ alkyl or a member of a fused ring wherein the fused ring is a substituted or unsubstituted, saturated or unsaturated, five or six-membered, heterocyclic or carbocyclic ring fused to the A ring comprising R₁₀, the carbon atom to which R₁₀ is attached, R₂₀, and the nitrogen atom to which R₂₀ is attached;

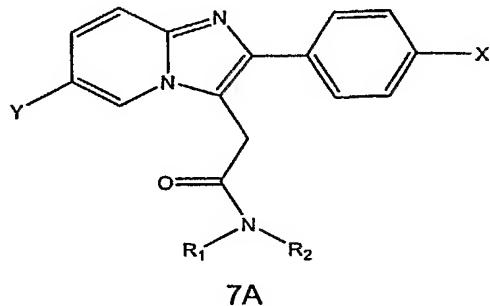
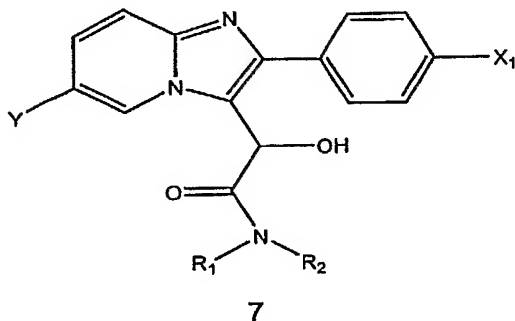
R₂₁ is hydrogen, halogen or C₁₋₄ alkyl;

n is 0 or 1;

each Y is independently hydrogen, halogen or C₁₋₄ alkyl; and

when Z is CR₂₁, the A ring is aromatic.

2. The process of claim 1 wherein the heteroaryl α -hydroxyacetamide has the structure of Formula 7 and the heteroaryl acetamide has the structure of Formula 7A



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wherein

Y is C₁₋₄ alkyl;

X₁ is C₁₋₄ alkyl; and

R₁ and R₂ are independently hydrogen or C₁₋₅ alkyl.

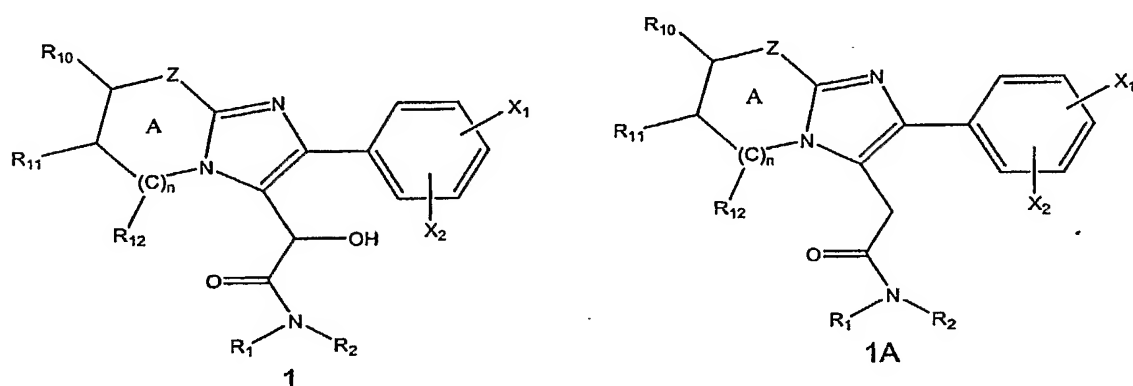
3. The process of claim 1 wherein the halide is bromide, the catalyst is palladium on carbon and the solvent system comprises acetic acid.

4. The process of claim 3 further comprising a water scavenger wherein the water scavenger is a carboxylic acid anhydride.

5. The process of claim 4 wherein the solvent system comprises acetic acid and the water scavenger is acetic anhydride.

6. The process of claim 5 wherein the heteroaryl α -hydroxyacetamide is α -hydroxyzolpidem and the heteroaryl acetamide is zolpidem.

7. A process for the preparation of a heteroaryl acetamide from a heteroaryl α -hydroxyacetamide, the process comprising forming a reaction mixture by combining a heteroaryl α -hydroxyacetamide, a strong acid, a halide, a catalyst and a water scavenger and contacting the reaction mixture with a hydrogen source, the heteroaryl α -hydroxyacetamide having the structure of Formula 1 and the heteroaryl acetamide having the structure of Formula 1A:



wherein

Z is O, NR₂₀ or CR₂₁;

X₁ and X₂ are independently selected from the group consisting of hydrogen, halogen, C₁₋₄ alkoxy, C₁₋₆ alkyl, -CF₃ and CH₃SO₂-;

R₁ and R₂ are independently hydrogen or hydrocarbyl;

R₁₀ is hydrogen, halogen, C₁₋₄ alkyl, or a member of a fused ring wherein the fused ring is (i) a substituted or unsubstituted, saturated or unsaturated, five or six-membered, heterocyclic or carbocyclic ring fused to the A ring comprising R₁₀, the carbon atom to which R₁₀ is attached, R₂₀, and the nitrogen atom to which R₂₀ is attached, or (ii) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R₁₀, R₁₁, and the carbon atoms to which R₁₀ and R₁₁ are attached, optionally substituted with Y at a substitutable position thereof;

R₁₁ is hydrogen, halogen, C₁₋₄ alkyl, or a member of a fused ring wherein the fused ring is (i) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R₁₀, R₁₁, and the carbon atoms to which R₁₀ and R₁₁ are attached, optionally substituted with Y at a substitutable position thereof, or (ii) a six-

membered, aromatic, carbocyclic ring fused to the A ring comprising R_{11} , R_{12} , and the carbon atoms to which R_{11} and R_{12} are attached, optionally substituted with Y at a substitutable position thereof;

R_{12} , if present, is hydrogen, halogen, C_{1-4} alkyl, or a member of a fused ring wherein the fused ring is (i) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R_{11} , R_{12} , and the carbon atoms to which R_{11} and R_{12} are attached, optionally substituted with Y at a substitutable position thereof;

R_{20} is C_{1-5} alkyl or a member of a fused ring wherein the fused ring is a substituted or unsubstituted, saturated or unsaturated, five or six-membered, heterocyclic or carbocyclic ring fused to the A ring comprising R_{10} , the carbon atom to which R_{10} is attached, R_{20} , and the nitrogen atom to which R_{20} is attached;

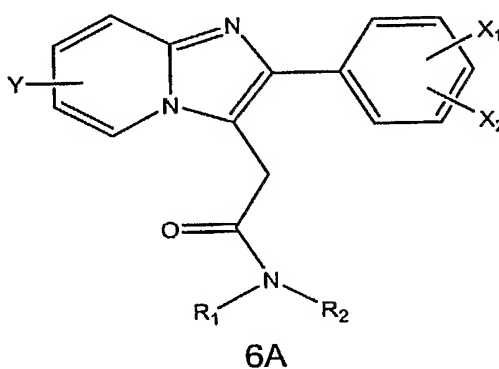
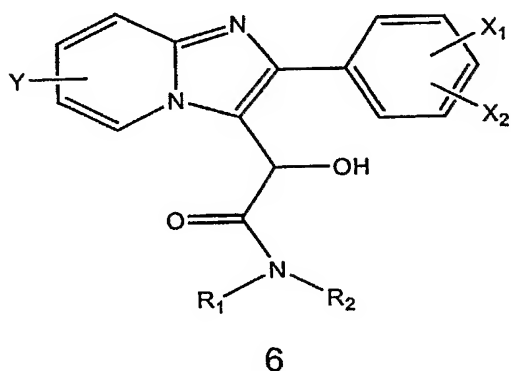
R_{21} is hydrogen, halogen or C_{1-4} alkyl;

n is 0 or 1;

each Y is independently hydrogen, halogen or C_{1-4} alkyl; and

when Z is CR_{21} , the A ring is aromatic.

8. The process of claim 7 wherein the heteroaryl α -hydroxyacetamide has the structure of Formula 6 and the heteroaryl acetamide has the structure of Formula 6A



wherein

Y is hydrogen, halogen or C_{1-4} alkyl;

X_1 and X_2 are independently selected from the group consisting of hydrogen, halogen, C_{1-4} alkoxy, C_{1-6} alkyl, CF_3 and CH_3SO_2 ; and

R_1 and R_2 are independently hydrogen or C_{1-5} alkyl.

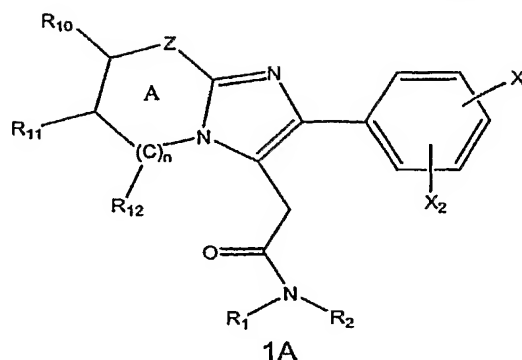
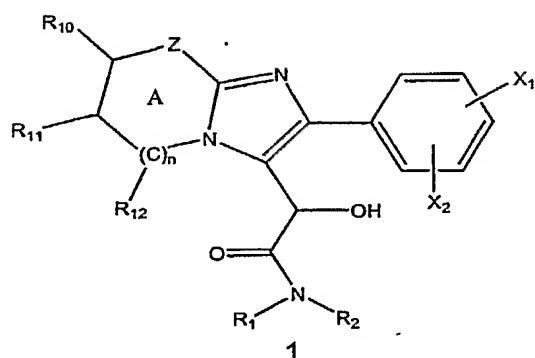
9. The process of claim 7 wherein more than 1.0 equivalent of the water scavenger per mole of water present in the reaction mixture is used to have excess water scavenger upon contact of the reaction mixture with the hydrogen source.

10. The process of claim 9 wherein the solvent system comprises a carboxylic acid and the water scavenger comprises the corresponding carboxylic acid anhydride.

11. The process of claim 10 wherein the heteroaryl α -hydroxyacetamide is α -hydroxyzolpidem and the heteroaryl acetamide is zolpidem.

12. The process of claim 11 wherein the strong acid is sulfuric acid, the halide is a bromide ion and the catalyst is palladium on carbon.

13. A process for the preparation of a heteroaryl acetamide from a heteroaryl α -hydroxyacetamide, the process comprising directly hydrogenating a heteroaryl α -hydroxyacetamide in the presence of hydrogen gas in a reaction mixture comprising a solvent system, the heteroaryl α -hydroxyacetamide, at least one strong acid, a halide and a palladium on carbon catalyst, wherein the reaction mixture contains less than about 2.5 wt.% water, the heteroaryl α -hydroxyacetamide corresponding to Formula 1 and the heteroaryl acetamide product corresponding to Formula 1A:



wherein

Z is O, NR₂₀ or CR₂₁;

X_1 and X_2 are independently selected from the group consisting of hydrogen, halogen, C_{1-4} alkoxy, C_{1-6} alkyl, $-CF_3$ and CH_3SO_2- ;

R₁ and R₂ are independently hydrogen or hydrocarbyl;

R₁₀ is hydrogen, halogen, C₁₋₄ alkyl, or a member of a fused ring wherein the fused ring is (i) a substituted or unsubstituted, saturated or unsaturated, five or six-membered, heterocyclic or carbocyclic ring fused to the A ring comprising R₁₀, the carbon atom to which R₁₀ is attached, R₂₀, and the nitrogen atom to which R₂₀ is attached, or (ii) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R₁₀, R₁₁, and the carbon atoms to which R₁₀ and R₁₁ are attached, optionally substituted with Y at a substitutable position thereof;

R_{11} is hydrogen, halogen, C_{1-4} alkyl, or a member of a fused ring wherein the fused ring is (i) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R_{10} , R_{11} , and the carbon atoms to which R_{10} and R_{11} are attached, optionally substituted with Y at a substitutable position thereof, or (ii) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R_{11} , R_{12} , and the carbon atoms to which R_{11} and R_{12} are attached, optionally substituted with Y at a substitutable position thereof;

R₁₂, if present, is hydrogen, halogen, C₁₋₄ alkyl, or a member of a fused ring wherein the fused ring is (i) a six-membered, aromatic, carbocyclic ring fused to the A ring comprising R₁₁, R₁₂, and the carbon atoms to which R₁₁ and R₁₂ are attached, optionally substituted with Y at a substitutable position thereof;

R_{20} is C_{1-5} alkyl or a member of a fused ring wherein the fused ring is a substituted or unsubstituted, saturated or unsaturated, five or six-membered, heterocyclic or carbocyclic ring fused to the A ring comprising R_{10} , the carbon atom to which R_{10} is attached, R_{20} , and the nitrogen atom to which R_{20} is attached;

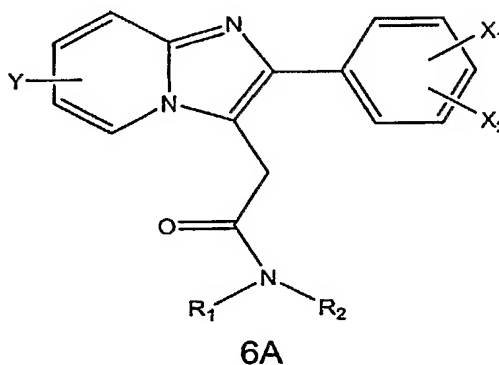
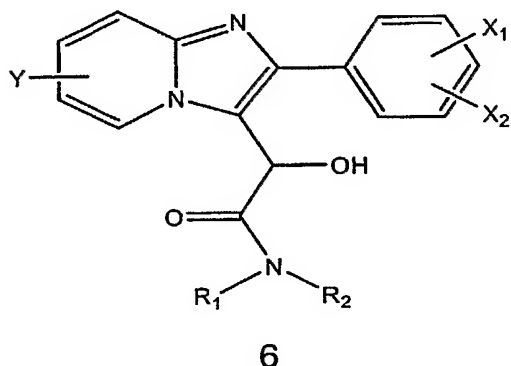
R_{21} is hydrogen, halogen or C_{1-4} alkyl;

n is 0 or 1;

each Y is independently hydrogen, halogen or C_{1-4} alkyl; and

when Z is CR_{21} , the A ring is aromatic.

14. The process of claim 13 wherein the heteroaryl α -hydroxyacetamide has the structure of Formula 6 and the heteroaryl acetamide has the structure of Formula 6A



wherein

Y is hydrogen, halogen or C_{1-4} alkyl;

X_1 and X_2 are independently selected from the group consisting of hydrogen, halogen, C_{1-4} alkoxy, C_{1-6} alkyl, CF_3 and CH_3SO_2 ; and

R_1 and R_2 are independently hydrogen or C_{1-5} alkyl.

15. The process of claim 13 further comprising a water scavenger.

16. The process of claim 15 wherein the heteroaryl α -hydroxyacetamide is α -hydroxyzolpidem and the heteroaryl acetamide

is zolpidem, the strong acid is sulfuric acid, the halide is a bromide ion, the solvent system comprises acetic acid and the water scavenger is acetic anhydride.

17. The process of claim 13 wherein the reaction mixture contains less than about 1.0 wt.% water at initiation of hydrogenation.

18. The process of claim 16 wherein the reaction mixture contains less than about 0.1 wt.% water at initiation of hydrogenation.

19. The process of claim 13 wherein the reaction mixture contains less than about 1.0 wt.% during hydrogenation.

20. The process of claim 16 wherein the reaction mixture contains less than about 0.1 wt.% during hydrogenation.